COLUMBIA UNIVERSITY MEDICAL CENTER

DEPARTMENT OF PSYCHIATRY
1051 RIVERSIDE DRIVE
NEW YORK, NY 10032

July 24, 2012

Robert Haddad, Esq.
Shuttleworth, Ruloff, Swain, Haddad & Morecock, PC
Southport Center
4525 South Boulevard
Suite 300
Virginia Beach, VA 23452

Dear Mr. Haddad,

At your request, I have reviewed the case of Kelli Grese. The following report represents my opinions regarding the extent to which the Veterans Administration and its employees failed to conform to the standard of care in rendering psychiatric care to her, and related issues in this case. To prepare this report, I reviewed the records of her treatment at the Veterans Affairs Medical Centers at Hampton and Salem from June 2, 1998 to December 8, 2010; records of her treatment at the Virginia Beach Psychiatric Center from September 1, 2001 to October 8, 2010; the report of her autopsy; a copy of the diary that Ms. Grese kept during January 2010; an email sent by Ms. Grese to her mother on November 8, 2010; the Initial Disclosures and discovery responses and documents provided by Defendant United States of America; and the depositions of Dr. McDaniel and Mr. Mui. The opinions that follow are based on my review of this material, the studies cited in the body of this report, and my more than 30 years as a practicing psychiatrist.

Summary of Psychiatric History: Kelli Grese, at the time of her death, was a 37 year-old woman with a roughly 15-year history of significant psychiatric problems. Over those years, she received multiple psychiatric diagnoses, most notably post-traumatic stress disorder (PTSD), bipolar disorder with psychotic features, schizoaffective disorder, attention deficit hyperactivity disorder (ADHD), and polysubstance abuse. Ms. Grese was treated with multiple psychotropic medications; at the time of her last discharge from the VA Hampton Residential Treatment Facility, these included total daily doses of quetiapine 300 mg, carbamazepine 400 mg, gabapentin 900 mg, and a 24-hour nicotine patch 21 mg.

The last year of Ms. Grese's life was particularly tumultuous. She began a diary during January 2010 that documented her desperation and the emptiness of her life, clear suicidal intent, and poor reality testing (e.g., expecting celebrities to respond to her messages to their Facebook pages). From January 8-14, 2010, she was admitted to the Virginia Beach Psychiatric Center with diagnosis of major depression

(recurrent, severe), PTSD, alcohol dependence, and polysubstance dependence. On March 12, 2010, Ms. Grese presented for domiciliary admission to the VAMC Hampton, but because of her condition was referred to the emergency room (ER). She was described as very paranoid, experiencing command auditory hallucinations, unable to control her abuse of prescription medication, and manifesting suicidal ideation. While in the ER, she consumed a large amount of quetiapine, leading her to become unresponsive. She was admitted to the hospital for treatment of a quetiapine overdose, and subsequently suffered a seizure and required admission to the medical intensive care unit (ICU). After a tumultuous course in the ICU, marked by signs of delirium and psychosis, and despite her use of quetiapine to overdose a few days before, on March 18, 2010, Ms. Grese was restarted on quetiapine by VA medical staff. On March 19, 2010, apparently because of the unavailability of a psychiatric bed at VAMC Hampton, she was transferred to the Virginia Beach Psychiatric Center, and then on March 23, 2010 was transferred back to VAMC Hampton, prior to her discharge on March 25, 2010. Her discharge medications from the VA included a total daily dose of 600 mg of quetiapine.

Approximately one-and-a-half months later, on May 9, 2010, Ms. Grese again overdosed on "a handful" of quetiapine. This time, rescuers had to break into her car to assist her, and she was again hospitalized at Virginia Beach Psychiatric Center. She was described as having some degree of paranoia, racing thoughts, flight of ideas, hopelessness, helplessness, and feelings of guilt and worthlessness. On May 13, 2010, Ms. Grese was discharged from Virginia Beach Psychiatric Center, having been restarted on quetiapine at a total daily dose of 250 mg.

A VAMC Hampton telephone encounter note dated June 22, 2010 reported that Ms. Grese had just returned to the area after being discharged from an unnamed hospital in Pittsburgh. Once more, she reported that she had overdosed on quetiapine and had to be hospitalized in an ICU. No other details of this hospitalization are reported. However, at the time of the call it appears that she again was taking quetiapine and no effort was made by the VA staff to alter her treatment. For reasons that are unclear, despite her recent, self-reported suicidality, there was no further VA contact with the patient until July 28, 2010, when she was seen for a screening assessment for inpatient substance abuse treatment. On July 30, 2010, a suicide assessment report was entered into Ms. Grese's record; it noted her repeated suicide attempts with quetiapine and among the approaches that it called for was to "limit the means" available to her. However, no effort was made to alter her medication treatment. A "Suicide Review Mental Health Clinical Warning" note on August 1, 2010 recorded a (somewhat inaccurate) warning that she had twice overdosed in March on large amounts of quetiapine.

Despite this history, a medical clearance note on August 4, 2010, prior to her admission to a VA domiciliary substance abuse treatment program, indicated that her current outpatient medications again included quetiapine 300 mg at bedtime, which was continued during her entire time in the program. Sixty-day prescriptions for quetiapine were filled at VAMC Hampton twice within a 2-day period, on October

19 and 20, 2010. The October 19th order was being sent by mail to Ms. Grese from a central VA pharmacy in South Carolina when she appeared in person on October 20th to request that her quetiapine be dispensed to her directly. This is exactly what the pharmacist at VA Hampton then did. The pharmacist, Mr. Mui, denies having had contact with Ms. Grese's psychiatrist, Dr. McDaniel, before dispensing the medication; however, Dr. McDaniel maintains that he contacted the pharmacist and that the prescription was dispensed at his urging, because the patient told him that she was planning to leave town immediately. Ms. Grese was discharged from the domiciliary program on October 20, 2010. At that time she was judged to be at low risk for suicide. After attending two weekly outpatient groups, the only follow up she had after her discharge, she did not appear for group therapy on November 10, 2010, the last day on which she had contact with her sister. Two days later, November 12, 2010, she was found dead at her bedside; with her were an empty container of quetiapine and a second mostly empty container. An autopsy report indicated that she died of acute quetiapine overdose, with a blood level of 8.4mg/liter, 20-100 times the therapeutic level, and well above the level that is likely to be fatal. Material was found in her stomach that appeared to be the residue of quetiapine pills.

Impressions: Kelli Grese was a woman with a chronic, complicated psychiatric history, marked by post-traumatic stress disorder; a psychotic mood disorder alternately diagnosed as bipolar disorder or schizoaffective disorder; and polysubstance abuse. She also experienced multiple psychosocial stresses. Over the last, tumultuous year of her life, she experienced four documented and one reported hospitalization, and prolonged residential treatment for substance abuse. Two of the documented admissions and the one reported hospitalization in Pittsburgh were precipitated by serious suicide attempts with quetiapine, apparently driven by her recurrent psychotic ideation, exacerbated by substance abuse, and resulting in serious medical complications requiring ICU care. Nonetheless, after each suicide attempt, she was restarted on quetiapine, the medication that she ultimately used to end her life.

It is my opinion, to a reasonable medical certainty, that the Department of Veterans Affairs and its employees fell below the applicable standard of care for the psychiatric treatment of Ms. Grese in the following ways:

1) VA staff, including Dr. McDaniel, failed to prescribe appropriately for Ms. Grese.

a) Quetiapine was an inappropriate choice for Ms. Grese's treatment. Of all the available antipsychotic medications, it is the only one that is reported to have abuse potential and, as a result, is sought by persons with a proclivity for substance abuse. (See, e.g., Pinta ER, Taylor PE. Quetiapine abuse? American Journal of Psychiatry 2007;164(1):174-175; Pierre JM, et al. Intranasal quetiapine abuse. American Journal of Psychiatry 2004;161(9): 1718; Waters BM, Joshi KG. Intravenous

quetiapine-cocaine use ("Q-ball"). American Journal of Psychiatry 2007;164(1): 173-174; Murphy D, et al. Addictive potential of quetiapine. American Journal of Psychiatry 2008;165:918.) Given her extensive history of substance abuse, as well as reports of her drug-seeking behavior in relation to quetiapine, it should never have been prescribed for her, as it was likely that it would reinforce her drug-abusing behavior.

b) Quetiapine is a particularly problematic medication for suicidal patients, which is an additional reason why it should not have been prescribed for Ms. Grese, or at the very least should have been stopped when it was clear that she was engaging in life-threatening suicidal behavior with quetiapine. The largest review to date of the toxicity of antipsychotic medications showed that quetiapine was the most commonly used antipsychotic medication in overdoses reported to the California Poison Control System. Quetiapine had the highest rate of respiratory depression in overdose, and all 3 deaths in this series of almost 2000 cases were associated with ingestions of quetiapine. (Ciriani MA, Kearney TE, Olson KR. Comparing acute toxicity of first- and second-generation antipsychotic drugs: a 20-year, retrospective cohort study. Journal of Clinical Psychiatry 2009;70(1):122-129.) It is also known to prolong the heart's QT interval, which increases the risk of fatal cardiac arrhythmias.

c) When a patient engages in a serious suicide attempt by a particular means, every effort should be made to restrict their access to that means. Despite Ms. Grese's repeated, serious attempts to end her life with quetiapine, VA medical staff, including Dr. McDaniel, repeatedly continued to prescribe that medication for her, until she used it to end her life. Indeed, there is no evidence in the medical record that Dr. McDaniel or other VA medical staff caring for Ms. Grese ever considered the possibility of taking her off quetiapine, despite a note written the summer before she died indicating that restricting access to the means of suicide was an element of her management plan, and substituting another medication that was likely to be equally or more effective.

2) VA staff, specifically Dr. McDaniel, failed to appropriately assess and treat Ms. Grese's chronic suicidality. The medical record clearly documents that this was a patient who was subject to ongoing bouts of hopelessness that were exacerbated by significant psychotic symptoms, including auditory command hallucinations ordering her to kill herself. The recurrence of suicidality was predictable and called for continuous preventive measures. However, at the time of her discharge from the domiciliary program, the only apparent follow up was weekly group therapy for substance abuse and intermittent psychiatric visits for renewal of her prescriptions. There does

not appear to have been a plan in place for treatment of her multiple other psychiatric disorders or her recurrent suicidality.

3) VA staff, including Dr. McDaniel, negligently prescribed and dispensed Ms. Grese's quetiapine prescription twice within three days. Per the Initial Disclosures of Defendant United States of America, an October 19th order for quetiapine 300 mg, #60, 1 tab po qhs was being sent by mail to Ms. Grese from a central VA pharmacy in South Carolina when she appeared in person on October 20th to request that her quetiapine be dispensed to her directly, which it was. Given that a 60-day supply of the medication was on its way to Ms. Grese when the second 60-day supply was dispensed, she should not have been permitted to receive that second prescription. The pharmacist, Mr. Mui, maintains that he did that on his own initiative, without consultation with her psychiatrist. Assuming that to be the case, the pharmacist should have contacted the prescribing physician for authorization. If he had, given that Ms. Grese had already tried to end her life with a quetiapine overdosage on several occasions, her request should have been denied. At most, a several day supply should have been ordered to tide her over until her medication arrived by mail. The progress note by Johnny McCall dated October 18, 2010 indicates that the request originated with Ms. Grese, who "Requests larger Rx so she won'g [sic] be at risk of running oot [sic] of meds as often," a request that—given her history of suicidality—should have been denied.

In his deposition, however, Dr. McDaniel indicates that he spoke directly to the pharmacist to urge that the additional quetiapine be dispensed to Ms. Grese. He indicates that his reason was based on her claim that she intended to leave the area immediately after discharge, before the medications could arrive by mail. Additionally, she wanted to avoid the bother of refilling her prescription in another city. Given the near-lethal use that the patient made of prescribed quetiapine multiple times in the past, the standard of care called for him to exercise great care to not make available to her excessive amounts of the drug. Thus, he could have encouraged to remain in town until the medications arrived by mail, or simply to have refilled her current prescription when it expired, even if she were out of town. Failure to conform to the standard of care allowed Ms. Grese to stockpile a large amount of quetiapine, which was then available to her to end her life.

These failures to conform to the standard of care, in my opinion, were directly causative of Ms. Grese's death by quetiapine overdose.

In addition, you asked me to offer my opinion on Ms. Grese's mental state at the time of her suicide. Although no one can know with certainty what she was thinking at the moment that she consumed the fatal overdose of quetiapine, my opinion is that it is more likely than not that Ms. Grese was not capable of making a rational decision regarding ending her life. That opinion is based on two bodies of evidence. First, Ms. Grese's past suicide events were associated with and driven by psychotic

symptoms, including paranoia and command hallucinations ordering her to end her life by quetiapine overdosage. It is more likely than not that the same confluence of symptoms occurred when she took her fatal overdose. Second, based on the email that she sent to her mother on November 8, 2010, Ms. Grese was experiencing paranoid psychotic ideation about the Central Intelligence Agency, which had been a recurring theme when she was psychotic. This provides additional evidence that she had again succumbed to her recurrent psychotic symptoms shortly before she ended her life.

Qualifications: I am certified by the American Board of Psychiatry and Neurology in Psychiatry and in Forensic Psychiatry. I have practiced psychiatry, actively treating patients, for the last 32 years. In addition, I have taught and conducted research on psychiatry for that entire period. I am often consulted by colleagues on the management of suicidal patients, and I frequently review malpractice cases involving suicidality.

Since 2006, I have served as the Elizabeth K. Dollard Professor of Psychiatry, Medicine, and Law, and Director, Division of Law, Ethics, and Psychiatry, Department of Psychiatry, College of Physicians and Surgeons of Columbia University. I am also an affiliated faculty member at Columbia Law School, where one of the courses that I teach is Mental Health Law. From 1985-2005, I was the A.F. Zeleznik Professor of Psychiatry and Director of the Law and Psychiatry Program at the University of Massachusetts Medical School; in addition, from 1992-2005, I served as Chairman of the Department of Psychiatry there. Prior to that, I held faculty positions at the University of Pittsburgh Schools of Medicine and Law, and at Harvard Medical School, and was a Visiting Interdisciplinary Professor at Georgetown Law School.

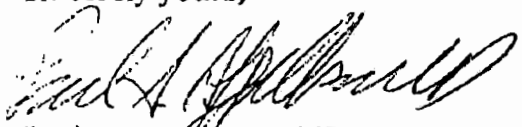
I am the author of many articles (over 230 peer-reviewed articles at this point) and books on law and ethics in clinical practice and research, including on the management of suicidal patients. From 2002 to 2003, I served as President of the American Psychiatric Association (APA), and from 1995 to 1996, I was President of the American Academy of Psychiatry and the Law. I have twice served 4-year terms as Chair of the Council on Psychiatry and Law for the APA, and I now chair APA's Committee on Judicial Action. I have been elected to the Institute of Medicine of the National Academy of Sciences, and received many awards for my work. I am a graduate of Columbia College, received my M.D. from Harvard Medical School, and completed my residency in psychiatry at the Massachusetts Mental Health Center/Harvard Medical School in Boston.

A list of my publications over the last ten years is appended to this report (Appendix A).

Previous Expert Testimony: A list of all the cases in which, during the last four years, I have testified as an expert at trial or by deposition is also appended to this report (Appendix B).

Compensation: I am being compensated at the rate of $500/hour for my work on this case.

Sincerely yours,



Paul S. Appelbaum, MD
Elizabeth K. Dollard Professor of Psychiatry, Medicine and Law
Director, Division of Law, Ethics, and Psychiatry
Columbia University

and rehabilitation. The patient endorsed daily use of intravenous cocaine mixed with 400 mg–800 mg of quetiapine. Quetiapine was surreptitiously diverted from his wife's prescription. He reported crushing the quetiapine tablets and mixing the resulting powder with cocaine and water. He subsequently heated the mixture and drew the supernatant through a cotton swab into a syringe to administer intravenously. When asked why he engaged in this drug mixture, he stated that it achieved desired "hallucinogenic" effects.

Combining prescription medications and/or illicit drugs is a common practice to synergistically heighten the intoxication from the substances while potentially reducing undesirable side effects. The combination of intravenous heroin and cocaine (also known as "speedball") is a well-known strategy to both maximize the cocaine "rush," while mitigating its "crash" (5). It may be hypothesized that quetiapine was substituted for heroin in our case (to form a "Q-ball") because the sedative/anxiolytic effects of quetiapine may mitigate the dysphoria associated with cocaine withdrawal and to possibly provide a "hallucinogenic" effect.

The case presented highlights the unknown effects (such as a "hallucinogenic" experience) of combining substances with different pharmacological properties and subsequently circumventing first-pass metabolism through intravenous administration. Individuals who use oral medications intravenously have the potential to develop significant pulmonary complications secondary to the deposition of medication binders in lung parenchyma. Furthermore, the cardiovascular and arrhythmogenic properties of cocaine may be amplified in combination with quetiapine (which has a risk of QTc prolongation). Physicians should remain cognizant of potential medication diversion and misuse in noncorrectional settings.

References

1. Hussain MZ, Waheed W, Hussain S: Intravenous quetiapine abuse (letter). Am J Psychiatry 2005; 162:1755–1756
2. Del Paggio D: Psychotropic medication abuse in correctional facilities. The Bay Area Psychopharmacology Newsletter 2005; 8:1, 5
3. Della Volpe K: Intervention reduces abuse of psychotropic medications in correctional facility. Pharmacy Practice News, July 2005
4. The Vaults of Erowid. http://www.erowid.org/ (accessed April 2006)
5. Smith JE, Co C, Coller MD, Hemby SE, Martin TJ: Self-administered heroin and cocaine combinations in the rat: additive reinforcing effects-supra-additive effects on nucleus accumbens extracellular dopamine. Neuropsychopharmacol 2006; 31: 139–150

BRIAN M. WATERS, M.D.
KAUSTUBH G. JOSHI, M.D.
San Antonio, Tex.

The authors report no competing interests.

Quetiapine Addiction?

TO THE EDITOR: Quetiapine is not a controlled substance and is not considered addictive. Yet there are several reports describing abuse among inmates in jails and prisons (1, 2).

The pharmaceutical formulary for the Ohio correctional system contains three second-generation antipsychotics, but quetiapine is not one of them. It may be prescribed with special authorization for patients with serious mental disorders who have not responded to formulary agents. However, inmates entering prison on quetiapine for other conditions, such as sleep and anxiety disorders, must have it tapered and discontinued.

The authors have treated a number of inmates who have engaged in drug-seeking and sometimes illegal behavior to obtain this medication. The following case is illustrative:

A 39-year-old incarcerated male with hepatitis C and a history of opiate abuse was treated for generalized anxiety disorder. When seen by the prison psychiatrist, he was receiving quetiapine 800 mg and clonidine 0.9 mg at bedtime.

The psychiatrist was concerned about the risks of prescribing an antipsychotic medication for a patient with hepatitis without a serious mental disorder. The patient refused to discuss other treatment alternatives stating, "I need my Seroquel." Efforts to enlist his cooperation for a quetiapine taper were unsuccessful. He abruptly left a treatment team meeting and informed staff that he would purchase quetiapine illegally from other inmates and had done this before.

We have treated other prisoners who have threatened [illegible] action and even suicide when presented with [illegible] of quetiapine. We have not seen similar drug-seeking behavior with other second-generation antipsychotics of comparable efficacy. Emil R. Pinta, M.D. has worked as a prison consultant for 35 years and can only recall similar behavior to obtain controlled substances.

Hussain et al. suggest that quetiapine abuse may be more prevalent among prisoners because commonly abused drugs are less readily available (2). Another reason may be that quetiapine treats anxiety and sleeplessness associated with substance use withdrawal—with prisoners having high rates for these disorders (3). However, an internet search yielded a number of self-reports by individuals who believe they have become addicted to this agent (4). There is a popular rap song in which "seroquel" is included in a long list of addictive substances (5). In street jargon, quetiapine is known as "quel" and "Susie-Q."

Our experience indicates the need for additional studies to explore the addiction-potential of quetiapine. Quetiapine is an effective medication for treatment of schizophrenia, bipolar disorder, and related illnesses. We believe clinicians should be extremely cautious when prescribing this medication for nonserious mental disorders and for individuals with histories of substance abuse.

References

1. Pierre JM, Shnayder I, Wirshing DA, Wirshing WC: Intranasal quetiapine abuse (letter). Am J Psychiatry 2004; 161:1718
2. Hussain MZ, Waheed W, Hussain S: Intravenous quetiapine abuse (letter). Am J Psychiatry 2005; 162:1755-1756
3. Monnelly EP, Ciraulo DA, Knapp C, Locastro J, Sepulveda I: Quetiapine for treatment of alcohol dependence. J Clin Psychopharmacol 2004; 24:532-535
4. Addiction to Seroquel. http://groups.msn.com/BipolarDisorderWeb Communnity/seroquel.msnw?action=get_message1

5. Lil' Wyte lyrics-Oxy Cotton lyrics. http://www.seeklyrics.com/lyrics/Lil-Wyte/Oxy-Cotton.html

EMIL R. PINTA, M.D.
Columbus, Ohio
ROBERT E. TAYLOR, M.D.
Cambridge, Ohio

The authors report no competing interests.

Safety of Aripiprazole: High Serum Levels in a CYP2D6 Mutated Patient

TO THE EDITOR: We present a patient with high serum levels of aripiprazole caused by a common genetic modification in CYP2D6.

A 51-year-old female patient diagnosed with schizophrenia was admitted to our clinic. Little antipsychotic effect being observed, the dose of aripiprazole was increased from 15 mg to 30 mg per day. Within approximately 2 weeks, progressive symptoms of lethargy and memory loss were evident.

After testing blood samples, the serum level of aripiprazole in our patient turned out to be 2990 ng/ml, approximately seven times the expected plasma concentration at the maximum dose of 30 mg per day (1).

Since aripiprazole is metabolized by CYP2D6 and CYP3A4 (2), testing for a genetic polymorphism in these genes was initiated, showing a substitution of G1934→A on both alleles of the CYP2D6 gene (homozygote CYP2D6*4/*4), corresponding with the suspected slow metabolism. Pharmacokinetic interactions with CYP3A4 were excluded, since our patient did not use concomitant medication, herbals or grapefruit juice. When aripiprazole was substituted by quetiapine 400 mg daily, the adverse symptoms improved.

The high serum levels of aripiprazole, not the adverse events, are disconcerting. Poor metabolization is seen frequently, with prevalence rates in Caucasians of 7% and of 1%–4% in Asians and black Americans (3, 4). Additionally, although aripiprazole is relatively safe in cases of acute intoxication (5), preclinical safety data revealed significant toxic effects in female rats, including 1) dose-dependent adrenocortical toxicity and 2) increased incidence of adrenocortical and combined carcinomas at three to 14 times, respectively, and 14 times the mean AUC at 30 mg a day (2). Our patient showed serum levels in the range of the toxic effects in animal studies. The concordance rate of toxicity in humans with animal studies is 71% (6). Assuming our patient to represent all poor metabolizers, many patients would potentially be at risk of long-term toxicity because of the good tolerability of aripiprazole (1).

Since poor metabolizing occurs regularly, we recommend drug monitoring (expected plasmaconcentration at 15 mg and 30 mg daily: 206-278 ng/ml and 320–584 ng/ml, respectively [2]) after 14 days of treatment, when a steady state is expected as well as further safety studies in poor metabolizers.

References

1. Mallikaarjun S, Salazar DE, Bramer SL: Pharmacokinetics, tolerability, and safety of aripiprazole following multiple oral dosing in normal healthy volunteers. J Clin Pharmacol 2004; 44: 179–187
2. Bristol-Myers Squibb BV: Aripiprazole Summary of Product Characteristics, 2004
3. Evans WE, Relling MV, Rahman A, McLeod HL, Scott EP, Lin JS: Genetic basis for a lower prevalence of deficient CYP2D6 oxidative drug metabolism phenotypes in black Americans. J Clin Invest 1993; 91:2150–2154
4. Mizutani T: PM frequencies of major CYPs in Asians and Caucasians. Drug Metab Rev 2003; 35:99–106
5. Carstairs SD, Williams SR: Overdose of aripiprazole, a new type of antipsychotic. J Emerg Med 2005; 28:311–313
6. Olson H, Betton G, Robinson D, Thomas K, Monro A, Kolaja G, Lilly P, Sanders J, Sipes G, Bracken W, Dorato M, Van Deun K, Smith P, Berger B, Heller A: Concordance of the toxicity of pharmaceuticals in humans and in animals. Regul Toxicol Pharmacol 2000; 32:56–67

MARIEKE OOSTERHUIS, PHARMD.
GERBEN VAN DE KRAATS, M.D.
DIEDERIK TENBACK, M.D., PH.D.
Leiden, the Netherlands

All authors report no competing interests.

Comment on CME Courses

[I] wanted to pass on my thanks for this CME product. It's straightforward and easy to use. I am a military psychiatrist in Iraq for 6 mo[nths], and to know I can easily and cheaply pick up 3 CME hours per mo[nth] is a Godsend. Keep up the good work. Thanks again.

HENRY B. NELSON, M.D.
LSA Anaconda, Iraq

Corrections

In the Clinical Case Conference "An Interaction Between Aspirin and Valproate: The Relevance of Plasma Protein Displacement Drug-Drug Interactions" (Am J Psychiatry 2006; 163:1891–1896), the units for valproate blood levels were given as "ng/ml." They should be "μg/ml."

In the article "Differences in Brain Chemistry in Children and Adolescents With Attention Deficit Hyperactivity Disorder With and Without Comorbid Bipolar Disorder: A Proton Magnetic Resonance Spectroscopy Study" (Am J Psychiatry 2006; 163:316–318),the NIMH grant number in the acknowlegments should have been MH-01978.

References

1. American Psychiatric Association: Practice Guideline for the Treatment of Patients With Schizophrenia, second edition. Am J Psychiatry 2004; 161(Feb suppl)
2. Miller AL, Chiles JA, Chiles JK, Crismon ML, Rush AJ, Shon SP: The Texas Medication Algorithm Project (TMAP) schizophrenia algorithms. J Clin Psychiatry 1999; 60:649–657
3. Treatment of schizophrenia 1999: the Expert Consensus Guideline Series. J Clin Psychiatry 1999; 60(suppl 11):3–80

THEODORE J. WILF, M.D.
Glen Mills, Pa.

Intranasal Quetiapine Abuse

TO THE EDITOR: We would like to report on the widespread "abuse" of quetiapine among inmates in the Los Angeles County Jail—"the largest mental health institution in the world." Anecdotal reports from clinicians and staff estimate that as many as 30% of the inmates seen in psychiatric services report malingered psychotic symptoms (typically endorsing "hearing voices" or ill-defined "paranoia") in order to specifically obtain quetiapine. A history of substance dependence is common among those engaging in this practice. In addition to oral administration, the drug is also taken intranasally by snorting pulverized tablets. Such abusive self-administration seems to be driven by quetiapine's sedative and anxiolytic effects (to help with sleep or to "calm down") rather than by its antipsychotic properties. Accordingly, the drug has a "street value" (it is sold to other inmates for money) and is sometimes referred to simply as "quell."

Although the prevalence of this behavior beyond this narrow forensic population is unknown, the possibility of such an abuse potential is both curious and clinically pertinent. For example, it suggests that quetiapine is indeed associated with a better subjective response than its conventional antipsychotic counterparts (1). It also appears to give lie to the clinical myth that only psychotic patients will ask for and take antipsychotic medications. In our collective clinical experience, many patients (in particular, those with substance dependence) complain of "hearing voices" in order to procure hospital admission, disability income, or psychotropic medications (2). The "voices" are usually vague, highly suggestive of malingering (3), and occur in the absence of other symptoms (such as clear-cut delusions or thought disorganization) that would warrant a diagnosis of schizophrenia. While antipsychotic medications are not typically recognized as drugs with abuse potential, the use of intranasal quetiapine suggests otherwise and underscores the importance of recognizing malingered psychosis in clinical settings. This phenomenon is reminiscent of the era before the widespread use of atypical antipsychotic compounds, when a select group of patients would inappropriately seek and self-administer not only anticholinergics, such as trihexyphenidyl (4), but also low-potency antipsychotics, such as thioridazine or chlorpromazine. Finally, since the monosymptomatic "voices" endorsed by patients are often assumed to represent psychosis and therefore lead to reflexive prescription of antipsychotic medications, further investigative efforts aimed at distinguishing this clinical presentation from schizophrenia would be useful. If these entities could be reliably disentangled, it would help to reduce the diagnostic heterogeneity of schizophrenia and the unnecessary exposure of patients to the potentially harmful side effects of antipsychotic medications.

References

1. Voruganti L, Cortese L, Oyewumi L, Cernovsky Z, Zirul S, Awad A: Comparative evaluation of conventional and novel antipsychotic drugs with reference to their subjective tolerability, side-effect profile and impact on quality of life. Schizophr Res 2000; 43:135–145
2. Pierre JM, Wirshing DA, Wirshing WC: "Iatrogenic malingering" in VA substance abuse treatment. Psychiatr Serv 2003; 54:253–254
3. Resnick PJ: The detection of malingered psychosis. Psychiatr Clin North Am 1999; 22:159–172
4. Buhrich N, Weller A, Kevans P: Misuse of anticholinergic drugs by people with serious mental illness. Psychiatr Serv 2000; 51: 928–929

JOSEPH M. PIERRE, M.D.
IGOR SHNAYDER, M.D.
DONNA A. WIRSHING, M.D.
WILLIAM C. WIRSHING, M.D.
Los Angeles, Calif.

Atomoxetine and Nonresponders to Stimulants

TO THE EDITOR: Atomoxetine has been recently introduced for the management of attention deficit hyperactivity disorder (ADHD) (1), and a vigorous campaign is ongoing to encourage physicians to write prescriptions for this drug. A media blitz is being directed to consumers, encouraging them to seek this medication. Before this expensive norepinephrine enhancer is used as a first-line medication to treat ADHD, its advantages relative to the generically prescribed stimulants need to be established. Ideally, a placebo-controlled blinded study model such as the one previously used by us to study another norepinephrine enhancer, imipramine (2), should be used. Because the costs of administering atomoxetine are about $90 per month and generic stimulants cost, on average, about $25 per month, atomoxetine's role as a first-line therapy should be supported by research.

With this in mind, we evaluated this drug effectiveness in our clinical program by employing measures used routinely to gather data in our program among children who were nonresponders to clinical trials of stimulants.

Seven patients were selected from our clinic (which was previously described [3]). Their average age was 10.5 years, and their IQ was 75.6. Their IQ is deemed average by the New York City Board of Education in its special education program, in which most children have an artificially deflated performance that is most likely consequent to comorbid learning disabilities. All patients were diagnosed with ADHD by using standard DSM-IV criteria. In accordance with the company's recommendations, we used doses of atomoxetine starting with 0.5 mg/kg/day for 3 days and then increased them up to 1.4 mg/kg/day. Parents of the children consented to treatment in accordance with routine hospital procedure.

We measured behavioral changes at baseline (without drug) and at either 1.2 mg/kg/day or when behavioral exacerbation obligated discontinuation by using the 10-item hyperactivity index derived from the Conners Teacher's Rating Scale (4).

In this open-label clinical observation of children taking atomoxetine, no change was seen. Tests performed between

tional hypodopaminergic state and upregulation of the postsynaptic D_2 receptors, of which stimulation by aripiprazole could result in exacerbation of the manic symptoms.

Although this case report adds to the literature on atypical results of atypical antipsychotics, caution needs to be used while interpreting the results, since aripiprazole is approved for the treatment of acute mania. Possible differences in response to aripiprazole in patients with bipolar affective disorder versus those with schizoaffective disorder need to be investigated. Furthermore, a drug screen was not performed to assure the patient's denial of substance abuse.

References

1. Young RC, Biggs JT, Ziegler VE, Meyer DA: A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978; 133:429–435
2. Aubry JM, Simon AE, Bertschy G: Possible induction of mania and hypomania by olanzapine or risperidone: a critical review of reported cases. J Clin Psychiatry 2000; 61:649–655
3. Nolan BP, Schulte JJ, Jr: Mania associated with initiation of ziprasidone. J Clin Psychiatry 2003; 64:336
4. DeLeon A, Patel NC, Crismon ML: Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. Clin Ther 2004; 26:649–666

PRASAD RAO PADALA, M.D.
STEVEN P. WENGEL, M.D.
FREDERICK PETTY, PH.D., M.D.
Omaha, Neb.

Dr. Petty is on the speakers' bureau for BMS and Lilly and has grant support from Forest, AstraZeneca, Pfizer, and Abbott. All other authors report no competing interests.

Hyperglycemia in a 7-Year-Old Child Treated With Aripiprazole

TO THE EDITOR: Aripiprazole is a new atypical antipsychotic drug for the treatment of schizophrenia/schizoaffective disorders and bipolar disorder in adults. Recent studies suggest effectiveness of aripiprazole with minimal severe side effects in children (1). We report a case of a 7-year-old child with hyperglycemia following initiation of aripiprazole.

The patient was an overweight 7-year-old male child with the diagnosis of attention deficit/hyperactivity disorder (ADHD), combined type, mood disorders, not otherwise specified, and a positive family history of type II diabetes mellitus. From ages 4 to 6, the patient's ADHD symptoms were treated with methylphenidate. At age 6, the patient had increasing mood and behavior problems, including verbal explosiveness and physical aggression. These symptoms stabilized by increasing the dose of methylphenidate to 54 mg per day.

Nine months after the increase in methylphenidate, the child had an exacerbation of mood lability and aggression. Methylphenidate was discontinued. Aripiprazole 2.5 mg was initiated. The child's weight was 34.7 kg, and body mass index was 21.0 (98th percentile for the child's age). He was prescribed 18 mg of atomoxetine, but took atomoxetine for 1 week. Within 4 weeks of aripiprazole as the only medication, the patient developed polydipsia, polyuria, and polyphagia and was evaluated in the emergency room. At admission, vital signs were normal, his blood pressure was 117/55, his glucose was 659 mg/dl (70–105 mg/dl), and he had mild ketonuria (15 mg/dl). Weight, height, and body mass index were 34 kg, 128 cm, and 20.5 (97th percentile for age), respectively. Pertinent lab studies included sodium 127 mmol/liter (133–145 mmol/dl), chloride 91 mmol/L (96–108 mmol/dl), triglycerides 255 mg/dl (74–199 mg/dl), and hemoglobin A1c 10% (4%–6%). Insulin/islet cell antibodies were <1.0U/ml (0.0–0.9U/ml). Aripiprazole was discontinued. The child was treated with NPH and Humalin insulin. He was discharged to go home in 3 days while receiving subcutaneous insulin. After 4 weeks of insulin therapy, blood sugars normalized and insulin was discontinued. Seven months after initial presentation, the child developed insulin-dependent diabetes.

To our knowledge, this is the first report of a child developing hyperglycemia following the initiation of aripiprazole. This case is presented to highlight the following questions: 1) Was there an association between the emergence of hyperglycemia and aripiprazole administration, and 2) was the initial episode of hyperglycemia coincidental with the use of aripiprazole? This case documents the importance of obtaining a family history, physical examination, and baseline and monitoring laboratory analyses when treating with antipsychotic medications (2). Further studies are necessary to determine the relationship between metabolic abnormalities and aripiprazole treatment in children.

References

1. Findling RL, Kaufmann R, Batterson JR, Sallee FR, Auby P, Nyilas M, et al: Tolerability of Aripiprazole in Children and Adolescents With Major Psychiatric Diagnoses. Toronto, American Academy of Child Adolescent Psychiatry, 2005
2. Cheng-Shannon J, McGough JJ, Pataki C, McCracken JT: Second-generation antipsychotic medications in children and adolescents. J Child Adolesc Psychopharmacol 2004; 14:372–394

DORA D. LOGUE, M.D., M.P.H.
NILDA GONZALEZ, M.D.
SONDRA D.K. HELIGMAN, M.D.
JUDITH V. MCLAUGHLIN, M.D.
HAROLYN M.E. BELCHER, M.D., M.H.S.
Baltimore, Md.

All authors report no competing interests.

Intravenous Quetiapine-Cocaine Use ("Q-Ball")

TO THE EDITOR: We have noted recent reports of quetiapine diversion and misuse among inmates in correctional settings where it is also called "quell" or "baby heroin" (1, 2). It is used orally, intranasally, and intravenously for its potent sedative and anxiolytic properties (1, 2). Inmates obtain quetiapine for illegitimate use by malingering of psychotic symptoms or obtaining it from other inmates. The high prevalence of substance use disorders in corrections and the secondary gain of serving out "easy time" with pharmacological assistance contribute to an underground economy of diverted psychoactive medications (3). Anecdotal reports from colleagues—as well as online testimonials—support the existence of quetiapine diversion and misuse in noncorrectional settings as well (4). The following case is an example of prescription medication diversion with concomitant illicit substance use seen in the local county hospital emergency room.

A 33-year-old married Caucasian male with a history of polysubstance dependence (cocaine, heroin, alcohol, benzodiazepines) reported to the local county hospital emergency room requesting assistance with drug detoxification

and rehabilitation. The patient endorsed daily use of intravenous cocaine mixed with 400 mg–800 mg of quetiapine. Quetiapine was surreptitiously diverted from his wife's prescription. He reported crushing the quetiapine tablets and mixing the resulting powder with cocaine and water. He subsequently heated the mixture and drew the supernatant through a cotton swab into a syringe to administer intravenously. When asked why he engaged in this drug mixture, he stated that it achieved desired "hallucinogenic" effects.

Combining prescription medications and/or illicit drugs is a common practice to synergistically heighten the intoxication from the substances while potentially reducing undesirable side effects. The combination of intravenous heroin and cocaine (also known as "speedball") is a well-known strategy to both maximize the cocaine "rush," while mitigating its "crash" (5). It may be hypothesized that quetiapine was substituted for heroin in our case (to form a "Q-ball") because the sedative/anxiolytic effects of quetiapine may mitigate the dysphoria associated with cocaine withdrawal and to possibly provide a "hallucinogenic" effect.

The case presented highlights the unknown effects (such as a "hallucinogenic" experience) of combining substances with different pharmacological properties and subsequently circumventing first-pass metabolism through intravenous administration. Individuals who use oral medications intravenously have the potential to develop significant pulmonary complications secondary to the deposition of medication binders in lung parenchyma. Furthermore, the cardiovascular and arrhythmogenic properties of cocaine may be amplified in combination with quetiapine (which has a risk of QTc prolongation). Physicians should remain cognizant of potential medication diversion and misuse in noncorrectional settings.

References

1. Hussain MZ, Waheed W, Hussain S: Intravenous quetiapine abuse (letter). Am J Psychiatry 2005; 162:1755–1756
2. Del Paggio D: Psychotropic medication abuse in correctional facilities. The Bay Area Psychopharmacology Newsletter 2005; 8:1, 5
3. Della Volpe K: Intervention reduces abuse of psychotropic medications in correctional facility. Pharmacy Practice News, July 2005
4. The Vaults of Erowid. http://www.erowid.org/ (accessed April 2006)
5. Smith JE, Co C, Coller MD, Hemby SE, Martin TJ: Self-administered heroin and cocaine combinations in the rat: additive reinforcing effects-supra-additive effects on nucleus accumbens extracellular dopamine. Neuropsychopharmacol 2006; 31: 139–150

BRIAN M. WATERS, M.D.
KAUSTUBH G. JOSHI, M.D.
San Antonio, Tex.

The authors report no competing interests.

Quetiapine Addiction?

TO THE EDITOR: Quetiapine is not a controlled substance and is not considered addictive. Yet there are several reports describing abuse among inmates in jails and prisons (1, 2).

The pharmaceutical formulary for the Ohio correctional system contains three second-generation antipsychotics, but quetiapine is not one of them. It may be prescribed with special authorization for patients with serious mental disorders who have not responded to formulary agents. However, inmates entering prison on quetiapine for other conditions, such as sleep and anxiety disorders, must have it tapered and discontinued.

The authors have treated a number of inmates who have engaged in drug-seeking and sometimes illegal behavior to obtain this medication. The following case is illustrative:

A 39-year-old incarcerated male with hepatitis C and a history of opiate abuse was treated for generalized anxiety disorder. When seen by the prison psychiatrist, he was receiving quetiapine 800 mg and clonidine 0.9 mg at bedtime.

The psychiatrist was concerned about the risks of prescribing an antipsychotic medication for a patient with hepatitis without a serious mental disorder. The patient refused to discuss other treatment alternatives stating, "I need my Seroquel." Efforts to enlist his cooperation for a quetiapine taper were unsuccessful. He abruptly left a treatment team meeting and informed staff that he would purchase quetiapine illegally from other inmates and had done this before.

We have treated other prisoners who have threatened legal action and even suicide when presented with discontinuation of quetiapine. We have not seen similar drug-seeking behavior with other second-generation antipsychotics of comparable efficacy. Emil R. Pinta, M.D. has worked as a prison consultant for 35 years and can only recall similar behavior to obtain controlled substances.

Hussain et al. suggest that quetiapine abuse may be more prevalent among prisoners because commonly abused drugs are less readily available (2). Another reason may be that quetiapine treats anxiety and sleeplessness associated with substance use withdrawal—with prisoners having high rates for these disorders (3). However, an internet search yielded a number of self-reports by individuals who believe they have become addicted to this agent (4). There is a popular rap song in which "seroquel" is included in a long list of addictive substances (5). In street jargon, quetiapine is known as "quell" and "Susie-Q."

Our experience indicates the need for additional studies to explore the addiction-potential of quetiapine. Quetiapine is an effective medication for treatment of schizophrenia, bipolar disorder, and related illnesses. We believe clinicians should be extremely cautious when prescribing this medication for nonserious mental disorders and for individuals with histories of substance abuse.

References

1. Pierre JM, Shnayder I, Wirshing DA, Wirshing WC: Intranasal quetiapine abuse (letter). Am J Psychiatry 2004; 161:1718
2. Hussain MZ, Waheed W, Hussain S: Intravenous quetiapine abuse (letter). Am J Psychiatry 2005; 162:1755-1756
3. Monnelly EP, Ciraulo DA, Knapp C, Locastro J, Sepulveda I: Quetiapine for treatment of alcohol dependence. J Clin Psychopharmacol 2004; 24:532-535
4. Addiction to Seroquel. http://groups.msn.com/BipolarDisorderWeb Communnity/seroquel.msnw?action=get_message1

5. Kugaya A, Sanacora G: Beyond monoamines: glutamatergic function in mood disorders. CNS Spectr 2005; 10:808–819

ANDREAS MENKE, M.D.
SUSANNE LUCAE, M.D., PH.D.
STEFAN KLOIBER, M.D.
SONJA HORSTMANN, M.D.
THOMAS BETTECKEN, M.D.
MANFRED UHR, M.D., PH.D.
STEPHAN RIPKE, M.D.
MARCUS ISING, PH.D.
BERTRAM MÜLLER-MYHSOK, M.D.
FLORIAN HOLSBOER, M.D., PH.D.
ELISABETH B. BINDER, M.D., PH.D.
Munich, Germany

Drs. Binder, Holsboer, Müller-Myhsok, and Uhr are the inventors of FKBP5, a novel target for antidepressant therapy (international publication number: WO 2005/054500) and polymorphisms in ABCB1 associated with a lack of clinical response to medicaments (international application number: PCT/EP2005/005194). Dr. Binder has received grant support from Pfizer and GlaxoSmithKline. Dr. Holsboer is a founder of and shareholder with Affectis. Dr. Müller-Myhsok has served as a consultant to Affectis. Drs. Menke, Lucae, Kloiber, Horstmann, Bettecken, Ripke, and Ising report no competing interests.

Supported by a grant from the Exzellenz-Stiftung of the Max Planck Society. Funded by the Federal Ministry of Education and Research (BMBF) in the framework of the National Genome Research Network (NGFN), FKZ01GS0481.

This letter (doi: 10.1176/appi.ajp.2008.08020274) was accepted for publication in March 2008.

Addictive Potential of Quetiapine

TO THE EDITOR: The feigning of symptoms in order to gain access to addictive substances is a veritable cliché in urgent care settings. However, malingering psychotic symptoms in order to secure antipsychotic medication is unusual and counterintuitive. The preclinical *sine qua non* of antipsychotic efficacy has been the ability of a compound to ablate or at least attenuate reward learning in animal models. These compounds are notoriously "dysphorogenic," devoid of abuse potential, and subjectively noxious to the degree that medication adherence is one of the preeminent challenges of treatment. The newer "atypical" antipsychotic compounds have generally improved on this subjective intolerability, which has led to the steadily expanding use of these compounds in nonpsychotic patient populations, targeting extrapsychotic symptom clusters such as anxiety, mood variability, and even pedestrian insomnia. We present a case report of an individual who demonstrated classic drug seeking behavior, compulsive drug use, and diversion for resale of the atypical antipsychotic compound quetiapine.

"Mr. A" was a 29-year-old divorced, unemployed, Caucasian man, with an unclear medical history, who presented himself as a walk-in to our acute psychiatric treatment unit with a medication refill request. He reported that he had been diagnosed with schizophrenia (for which he was being treated with quetiapine [600 mg nightly]) and the local police were disturbing his sleep by "electronically monitoring" his testicles. He received his "usual" dose of quetiapine and then slept soundly. On examination the following morning, Mr. A had become cagey about the details of his somatic preoccupation and, although still somnolent, he lacked evidence for either a thought or mood disturbance. His urine toxicology screen was negative. The profundity of his sedation prompted a pharmacy review, which revealed that he had been receiving different and excessive amounts of quetiapine from several sources during the past few months. Upon confrontation, he admitted to both the excessive use and sale ($3.00 per 100 mg tablet) of quetiapine.

Quetiapine has come to dominate the atypical antipsychotic market, primarily through its use in the technically "off label" circumstances described previously. The modestly sedating toxic profile and perceived absence of abuse liability of the drug have prompted many clinicians to use it in place of traditional benzodiazepines for anxiety and insomnia. There is currently an accumulating body of anecdotal evidence (1–3) regarding the type of patient described in our case report, which questions both the accuracy of perceptions about the use of quetiapine and the wisdom of treatment practices. If the current misuse of the compound continues or expands, then the abuse "signal" will predictably become more evident and could ultimately prompt federal regulators to declare quetiapine a controlled substance. Should such an unfortunate eventuality come to pass, we will be able to confidently lay the blame at the feet of our collective prescriptive imprudence.

References

1. Pierre JM, Shnayder I, Wirshing DA, Wirshing WC: Intranasal quetiapine abuse (letter). Am J Psychiatry 2004; 161:1718
2. Hussain MZ, Waheed W, Hussain S: Intravenous quetiapine abuse (letter). Am J Psychiatry 2005; 162:1755–1756
3. Pinta ER, Taylor RE: Quetiapine addiction? (letter) Am J Psychiatry 2007; 164:174–175

DAVID MURPHY, M.D.
KIMBERLY BAILEY, R.N.
MICHAEL STONE
WILLIAM C. WIRSHING, M.D.
Culver City, Calif.

The authors report no competing interests.

This letter (doi: 10.1176/appi.ajp.2008.08020277) was accepted for publication in March 2008.

Delirium Associated With Lamotrigine and Fluoxetine Treatment

TO THE EDITOR: The anticonvulsant lamotrigine has been increasingly utilized as a mood stabilizer after receiving approval by the Food and Drug Administration for the treatment of bipolar I disorder. Although there have been relatively few reports of toxicity, we report a case of delirium with lamotrigine use, which highlights the importance of cautious dose increase and attention to potential drug interactions.

"Ms. A" was a 35-year-old married, employed, Caucasian woman who had been treated for depression with fluoxetine (40 mg) over the past 5 years. She had no history of confusion, psychosis, or suicidality. Two months prior to admission to our intensive care unit, her psychiatrist added lamotrigine to her medication regimen to treat a mood instability characterized as a bipolar spectrum disorder, although she did not have bipolar I disorder. Her lamotrigine had been increased from 200 mg to 400 mg

Comparing Acute Toxicity of First- and Second-Generation Antipsychotic Drugs: A 10-Year, Retrospective Cohort Study

Michael A. Ciranni, M.D., Ph.D.;
Thomas E. Kearney, Pharm.D.; and Kent R. Olson, M.D.

Received April 22, 2008; accepted Nov. 4, 2008. From the Department of Psychiatry, New York University (Dr. Ciranni); California Poison Control System, San Francisco Division, and the Department of Clinical Pharmacy, University of California, San Francisco (Drs. Kearney and Olson); and the Division of Clinical Pharmacology, University of California, San Francisco (Dr. Olson).

Dr. Ciranni has previously received an American Psychiatric Association (APA)/Bristol-Myers Squibb fellowship in public psychiatry and an APA/Lilly resident research award. Drs. Kearney and Olson report no financial or other relationships relevant to the subject of this article.

Corresponding author and reprints: Michael Ciranni, M.D., Ph.D., Department of Psychiatry, New York University, 462 1st Ave., NBV 20N11, New York, NY 10016 (e-mail: Michael.ciranni@nyumc.org).

Objective: Second-generation antipsychotics (SGAs) are far more commonly used in the United States compared to first-generation antipsychotics (FGAs), but the relative safety of SGAs compared to FGAs following acute toxic ingestions has not been studied.

Method: A retrospective cohort study was performed by chart review of the California Poison Control System electronic database of 1975 cases from the 10-year period 1997 to 2006 involving patients aged 18 to 65 years who ingested a single SGA or FGA. Cases were coded for overall severity of adverse outcome as defined by the American Association of Poison Control Centers criteria and for presence of specific symptoms and treatments. Odds ratios were calculated between SGAs and FGAs for various symptoms, treatments, and outcome severity.

Results: Odds of a major adverse outcome or death were significantly higher for SGAs than FGAs (OR = 1.71, 95% CI = 1.09 to 2.71). Patients taking SGAs had higher odds of respiratory depression (OR = 2.39, 95% CI = 1.09 to 5.26), coma (OR = 2.18, 95% CI = 1.30 to 3.65), and hypotension (OR = 1.80, 95% CI = 1.23 to 2.63) compared to those taking FGAs but lower odds of dystonia (OR = 0.12, 95% CI = 0.08 to 0.19) or rigidity (OR = 0.30, 95% CI = 0.10 to 0.90).

Conclusion: SGAs appear no safer than FGAs in acute overdose. While neuromuscular symptoms appear less frequently with SGAs compared to FGAs, the relatively greater rates of central nervous system depression associated with SGA overdose may be more dangerous.

J Clin Psychiatry 2009;70(1):122–129

Pharmacologic treatment of schizophrenia in the United States is largely dominated by the use of "atypical," or second-generation, antipsychotics (SGAs), which now comprise 90% of the market share for antipsychotic drugs in the United States.[1] The increased use of SGAs over "typical," or first-generation, antipsychotics (FGAs), has been driven mainly by initial reports of the superior efficacy of SGAs[2,3] as well as their seemingly more benign side effect profile.[4] Compared to FGAs, whose D_2 receptor antagonism reduced psychotic positive symptoms but led to increased extrapyramidal signs and tardive dyskinesia,[5] the SGAs have lower D_2 receptor affinity but greater affinity for serotonin and norepinephrine receptors.[6] This difference in receptor affinities may account for the reduced incidence of extrapyramidal symptoms observed with SGA use, as well as their reputed efficacy in treating negative and cognitive symptoms of schizophrenia.[6]

However, recent studies have questioned the superior efficacy of SGAs over FGAs,[1,7] leading to a reappraisal of SGA use. Long-term use of SGAs may lead to lower rates of extrapyramidal symptoms compared to the FGAs,[8] but this risk appears to have been replaced by a greater tendency toward weight gain[9] as well as altered glucose[10] and lipid metabolism.[11] The relative safety of SGAs compared to FGAs in acute toxic ingestions has not been well studied. Most of the available data on SGA toxicity are based on case reports or case series involving individual SGAs,[8] preventing adequate comparison. Given that the lifetime risk for suicide among persons with schizophrenia is approximately 50% for suicide attempts and 10% for completed suicides,[12] the relative safety of SGAs compared to FGAs warrants further consideration.

The primary goal of this study was to compare the effects of SGAs and FGAs after acute toxic ingestion in a large number of adults as reported to a statewide regional poison control system in terms of symptoms, treatments, and overall severity of outcome. A secondary goal of this study was to examine the frequency with which specific symptoms and treatments were associated with specific SGAs or FGAs.

METHOD

Study Design and Case Selection

A retrospective cohort study was performed by chart review of the California Poison Control System (CPCS) electronic database for cases from the years 1997 through 2006. The CPCS provides treatment advice and referral assistance to the public and to health professionals through its toll-free emergency hotline 24 hours a day, 365 days a year, through 4 highly integrated sites operating under a single administration. Each reported poisoning case is entered prospectively into a clinical database (Visual Dotlab) by trained poison center specialists. The specialists are licensed as either a pharmacist or nurse with special training in clinical toxicology through a regional poison center. They are individually certified by the American Association of Poison Control Centers after passing a standardized national examination. In 2006 alone, the California Poison Control System consulted on 221,798 human poisoning exposure cases that were recorded in its case database.

The poison center specialists enter the initial and follow-up notes into a text field for individuals referred to a health care facility, and for each case enter specific symptom, treatment, and outcome codes according to American Association of Poison Control Centers (AAPCC) criteria.[13,14] Symptom and treatment codes are self-explanatory. Formal definition of the outcome codes is provided by the AAPCC.[13] In general, a minor effect is defined as having "symptoms that were minimally bothersome to the patient and resolve rapidly. The patient returned to a pre-exposure state of well being and had no residual disability or disfigurement."[13(p812)] A moderate effect is defined as having "symptoms which are more pronounced, more prolonged or more of a systemic nature than minor symptoms, but were not life-threatening and the patient had returned to a pre-exposure state of well-being with no residual disability or disfigurement."[13(p813)] A major effect is defined as having "symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement."[13(p813)]

Eligible cases involved adults aged 18 to 65 years with a reported ingestion of an FGA or an SGA who were referred to a health care facility for evaluation and treatment. Table 1 shows the FGAs and SGAs included in our database search. Cases were excluded if they did not receive treatment at a health care facility (e.g., were referred to a facility but never arrived or left against medical advice), if they involved a co-ingestion of another prescription drug, if they involved a co-ingestion of alcohol or a controlled substance, or if no definite outcome was recorded.

Table 1. First- and Second-Generation Antipsychotic Drugs Included in Search

First Generation	Second Generation
Benperidol	Amisulpride
Chlorpromazine	Aripiprazole
Chlorprothixene	Clozapine
Flupenthixol	Melperone
Fluphenazine	Olanzapine
Haloperidol	Quetiapine
Levomepromazine	Risperidone
Molindone	Sertindole
Mesoridazine	Sulpiride
Perphenazine	Ziprasidone
Pimozide	Zotepine
Prothipendyl	
Thioridazine	
Thiothixene	
Trifluoperazine	
Trifluopromazine	
Zuclopenthixol	

Coding of Symptoms, Treatments, and Adverse Outcomes

Data regarding all symptoms, treatments, and outcomes were extracted from the codes assigned to the cases by the poison center specialists as described above, with the exceptions of QT prolongation, wide QRS intervals, and neuroleptic malignant syndrome (NMS), for which there are no specific AAPCC codes. For QT prolongation and wide QRS intervals, one of the authors (M.A.C.) reviewed the text fields of the cases for the necessary information to define these conditions as present or absent using a priori definitions described below.

We classified a case as having a prolonged QT if a recorded QTc was greater than 430 milliseconds in men or 450 milliseconds in women.[15] If there was no QTc recorded but the QT and heart rate were recorded, we used Bazett's formula to calculate the QTc.[16] We also defined a case as having QT prolongation if the text field specifically mentioned a "prolonged" or "abnormal" QT. "Borderline" QTs were not included. Similarly, we classified a case as having a wide QRS if a QRS greater than 120 milliseconds was recorded,[17] if the text field specifically mentioned a "wide" or "abnormal" QRS, or if any kind of ventricular tachycardia was present. Text fields that did not include any QRS or QT information or any mention of an abnormal ventricular rhythm were assumed to have no QRS or QT abnormalities.

To find potential NMS cases, we focused our examination on cases in which fever, dystonia, rigidity, or rhabdomyolysis had already been coded in the database

as a symptom. We classified the potential NMS cases as being a "possible," "likely," or "unlikely" NMS case using criteria adapted from the research definitions from the DSM-IV-TR.[18] To qualify as a possible NMS case, the text field of a potential case had to specifically mention (1) stiffness or rigidity described concurrently with (2) an elevated temperature, either with text or with a recorded temperature greater than 38°C or 100.4°F. Cases that described elevated temperature without concurrent rigidity or stiffness, or vice versa, were classified as unlikely NMS cases. The possible NMS cases were upgraded to likely NMS if (1) the text field described 2 of the 10 possible additional symptoms as defined by criterion B of the DSM-IV research definition of NMS,[15] i.e., diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, or laboratory evidence of muscle injury (e.g., elevated creatine phosphokinase) and (2) there was no alternative diagnosis that was as or more likely to explain the fever and other associated findings. The cases that were not potential NMS cases (i.e., did not have fever, dystonia, rigidity, or rhabdomyolysis as one of the assigned symptom codes) were all classified a priori as unlikely NMS cases without further review. Two of the authors (M.A.C. and K.R.O.) independently classified all the potential NMS cases. Cases that had discrepancies in classification between the first 2 authors were resolved by the third author's (T.E.K.) independent review and classification of the case.

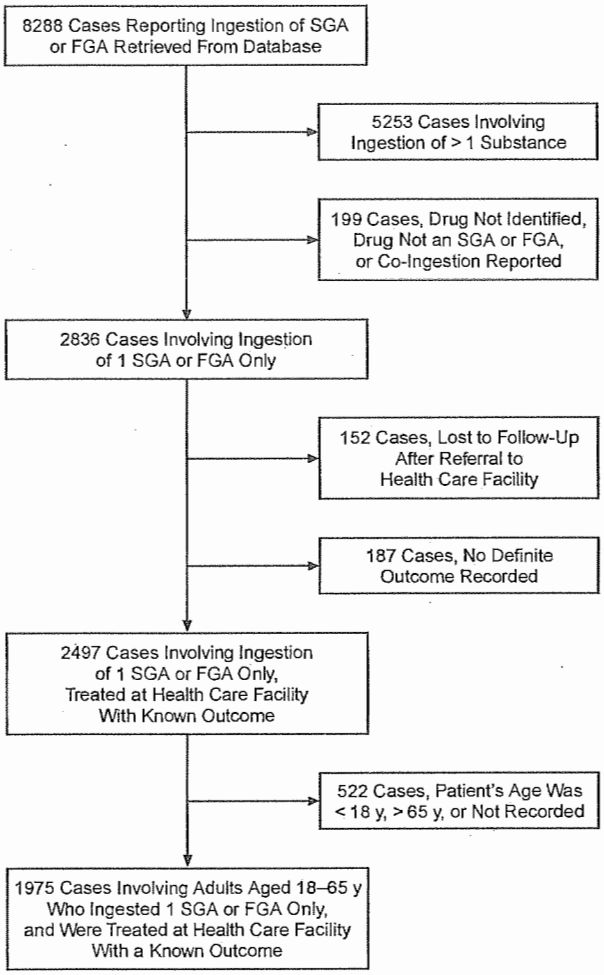
To find potential serotonin syndrome cases, we focused our evaluation on all the potential NMS cases using the symptom coding criteria above, and all cases in which tremor had already been coded as a symptom in the database. We evaluated the clinical information provided in the text field of a potential serotonin syndrome case and applied the Hunter Serotonin Toxicity Criteria decision rules[19] to these potential cases in order to classify them as cases of serotonin syndrome or not. Two of the authors (M.A.C. and K.R.O.) reviewed the potential cases and applied the decision rules independently, with discrepant classifications resolved by the third author's (T.E.K.) independent review and classification of the case.

RESULTS

Selection of Cases for Analysis

Figure 1 shows the selection process for cases that would ultimately be examined in this study. Initially extracted from the database were 8288 cases involving people who had ingested an antipsychotic (FGA or SGA) and were referred to a health care facility. Of those initial cases, 5253 cases involved ingestion of more than 1 substance and were excluded from further analysis. Of the remaining cases, 199 were removed if, on further review, the target drug was not an FGA or SGA, the target drug could not be specifically identified, or a co-ingestion was identified. Another 152 cases were eliminated in which the patient was lost to follow-up after referral to a health care facility. An additional 187 cases were excluded from analysis because no definite outcome of the case was recorded. Finally, 522 cases were excluded in which the patient's age fell outside the 18 to 65 year range or was not recorded, leaving 1975 cases for analysis. Of these, 936 cases (47.4%) were male, 1038 cases (52.6%) were female, and 1 case did not have a record of the gender. The proportion of males to females was not significantly different between FGAs and SGAs ($\chi^2 = 0.312$, df = 1). The mean age for males was 34.3 years, with a standard deviation (SD) of 11.1 years, and the mean age for females was 35.4 years, with an SD of 11.1 years. This difference in age between the sexes was significant ($F = 4.61$, df = 1,1970; $p < .05$); however, there were no overall differences in age between cases of FGA or SGA

Figure 1. Selection of Cases for Analysis



Abbreviations: FGA = first-generation antipsychotic, SGA = second-generation antipsychotic.

Table 2. Frequency (and percentage) of Adverse Outcomes and Deaths Associated With Second-Generation Antipsychotic (SGA) and First-Generation Antipsychotic (FGA) Use, N (%)

Adverse Outcome	SGA, N = 1568	FGA, N = 407
Minor adverse effect	716 (45.7)	197 (48.4)
Moderate adverse effect	706 (45.0)	187 (46.0)
Major adverse effect	143 (9.1)	23 (5.7)
Death	3 (0.2)	0 (0.0)

ingestion (F = 0.469, df = 1,1970), and the interaction of sex and type of drug ingested on age was not significant (F = 0.305, df = 1,1970). Other demographic information was not recorded.

Frequencies and Odds Ratios Between SGAs and FGAs for Adverse Outcomes

Table 2 shows the numbers of minor, moderate, or major adverse outcomes and deaths associated with SGA or FGA use, as well as the percentage of FGA or SGA cases involving that outcome. The odds of a major adverse outcome or death were significantly greater for the SGA cases (OR = 1.71, 95% CI = 1.09 to 2.71), as shown in the bottom row of Table 3. Of the 143 cases involving major adverse outcomes with SGAs, the most commonly associated symptoms were coma (75 cases), respiratory depression (31 cases), and seizures (11 cases). Of the 23 cases involving major adverse outcomes with FGAs, the most commonly associated symptoms were coma (11 cases), cardiac conduction disturbances (9 cases collectively), and possible or likely NMS (3 and 2 cases, respectively, or 5 cases overall). The 3 deaths reported all involved SGA ingestions, specifically quetiapine. One of the 3 deaths on autopsy appeared to be the result of an intracranial hemorrhage, not drug overdose (although no serum drug levels were obtained). The other 2 patients died of pulmonary complications secondary to aspiration pneumonia.

Frequencies and Odds Ratios Between SGAs and FGAs for Specific Symptoms and Treatments

Table 3 also shows the numbers of occurrences of each symptom or treatment for the FGAs and SGAs overall, as well as the percentage of FGA or SGA cases involving that symptom or treatment. The last column of the table shows the odds ratio and 95% confidence interval of each symptom or treatment occurring with an SGA. An OR with a 95% CI greater than 1 indicates the symptom or treatment was significantly more likely to occur with an SGA than with an FGA, whereas a 95% CI less than 1 indicates the symptom or treatment was significantly less likely to occur with an SGA compared to an FGA. For patients with SGA ingestions, there were significantly greater odds of developing respiratory depression (OR = 2.39, 95% CI = 1.09 to 5.26), coma (OR = 2.18, 95% CI = 1.30 to 3.65), or hypotension (OR = 1.80, 95% CI = 1.23 to 2.63) compared to those with FGA ingestions. In contrast, patients with FGA ingestions had significantly greater odds of developing dystonia (OR = 0.12, 95% CI = 0.08 to 0.19) or rigidity (OR = 0.30, 95% CI = 0.10 to 0.90) compared to those with SGA ingestions. The odds of rhabdomyolysis, fever, or seizure were not significantly different between patients taking SGAs and FGAs.

Only 249 cases (12.6%) had QT information available for analysis, and only 372 cases (18.9%) had QRS information reported. Using the assumption that cases with no QRS or QT information reported did not have any abnormalities, we did not find significantly different odds of developing a wide QRS or prolonged QT between SGAs and FGAs.

There were 245 cases that met criteria to be a potential NMS case and given further review. There was good agreement between the first 2 raters (99.2%, $\kappa = 0.89$) for the classification of potential NMS cases. Of the 245 cases, we found 4 likely and 0 possible NMS cases for the SGAs and 2 likely and 3 possible NMS cases for the FGAs. With the possible and likely NMS cases pooled together, the odds of showing symptoms concerning for NMS were significantly more likely with the FGAs than with the SGAs (OR = 0.21, 95% CI = 0.05 to 0.77). If the analysis was restricted to only the likely NMS cases, there were no differences in frequency of NMS between FGAs and SGAs (OR = 0.52, 95% CI = 0.09 to 2.84).

There were 267 cases that were given further review as potential serotonin syndrome cases. Agreement between the first 2 reviewers was 100% for the application of the Hunter Serotonin Toxicity Criteria. None of the cases reviewed met criteria as a serotonin syndrome case.

In terms of medical interventions used, SGA ingestions had significantly higher odds of involving intubation for airway protection during treatment (OR = 2.49, 95% CI = 1.69 to 3.86) as well as mechanical ventilation for respiratory compromise (OR = 2.79, 95% CI = 1.56 to 4.98). The odds of intravenous (IV) fluid use were significantly higher for the SGA cases (OR = 1.88, 95% CI = 1.44 to 2.46), but odds of vasopressor use did not differ between SGA and FGA cases.

Frequency of Specific Symptoms, Treatments, and Outcomes by Medication

Table 4 shows the number of cases involving each specific SGA or FGA included in the study. The most common SGAs reported in the study were quetiapine (939 cases), olanzapine (333 cases), and risperidone (220 cases), comprising 60%, 21%, and 14%, respectively, of the total SGA sample of 1568 cases. The most common FGAs reported in the study were chlorpromazine (117 cases), haloperidol (99 cases), and thioridazine (82 cases), comprising 29%, 24%, and 20%, respectively, of the total

Table 3. Odds Ratios for Specific Symptoms, Treatments, and Outcomes Associated With Second-Generation Antipsychotic (SGA) and First-Generation Antipsychotic (FGA) Use

Variable	SGA (N = 1569), N (%)	FGA (N = 407), N (%)	Odds Ratio (95% CI)
Respiratory depression	63 (4.0)	7 (1.7)	2.39 (1.09 to 5.26)
Coma	136 (8.7)	17 (4.2)	2.18 (1.30 to 3.65)
Hypotension	221 (14.1)	34 (8.4)	1.80 (1.23 to 2.63)
Long QT interval	73 (4.7)	28 (6.9)	0.66 (0.42 to 1.04)
Wide QRS interval	21 (1.3)	8 (2.0)	0.68 (0.30 to 1.54)
Dystonia	39 (2.5)	69 (17.0)	0.12 (0.08 to 0.19)
Rigidity	7 (0.5)	6 (1.5)	0.30 (0.10 to 0.90)
Rhabdomyolysis	8 (0.5)	3 (0.7)	0.69 (0.18 to 2.61)
Fever	13 (0.8)	6 (1.5)	0.56 (0.21 to 1.48)
Possible or likely NMS	4 (0.3)	5 (1.2)	0.21 (0.05 to 0.77)
Seizure	30 (1.9)	4 (1.0)	1.97 (0.69 to 5.61)
Intubation	212 (13.5)	24 (5.9)	2.49 (1.69 to 3.86)
Ventilation	132 (8.4)	13 (3.2)	2.79 (1.56 to 4.98)
Intravenous fluids	500 (31.9)	81 (19.9)	1.88 (1.44 to 2.46)
Vasopressors	25 (1.5)	5 (1.2)	1.30 (0.50 to 3.42)
Major adverse outcome or death	146 (9.3)	23 (5.7)	1.71 (1.09 to 2.71)

Abbreviation: NMS = neuroleptic malignant syndrome.

FGA sample of 407 cases. The 2 zuclopenthixol cases were the only cases in our study that involved an antipsychotic not commercially available in the United States. For each SGA or FGA, Table 4 also shows the number and percentage of cases involving that specific SGA or FGA in which a particular symptom or treatment was associated with it. For the 3 most frequently occurring SGAs, the 2 most commonly reported symptoms were as follows: quetiapine, hypotension (165 cases, 17.6%) and coma (96 cases, 10.2%); olanzapine, coma (34 cases, 10.2%) and hypotension (21 cases, 6.3%); and risperidone, hypotension (29 cases, 13.2%) and dystonia (19 cases, 8.6%). For the 3 most frequently occurring FGAs, the 2 most commonly reported symptoms were as follows: chlorpromazine, hypotension (10 cases, 8.6%) and coma (8 cases, 6.8%); haloperidol, dystonia (39 cases, 39.4%) and hypotension (8 cases, 8.1%); and thioridazine, long QT (14 cases, 17.1%) and hypotension (10 cases, 12.2%). Direct comparison of symptom percentages between individual drugs is limited by the marked difference in frequency among the various drugs and is also limited by misleading percentages created by low numbers of cases for some drugs.

DISCUSSION

In this study, the 2 most commonly occurring SGAs, quetiapine and olanzapine, made up over 80% of the SGA sample. Both drugs have significant histamine receptor blockade associated with central nervous system (CNS) depression.[8] Therefore, it is not surprising that higher rates of respiratory depression were observed in cases involving these drugs and that the odds of respiratory depression and coma would be greater overall for SGAs than for FGAs, given the prominence of these 2 drugs in the SGA sample. The higher odds of endotracheal intubation and mechanical ventilation for SGAs compared to FGAs are consistent with the higher rates of CNS depression observed with the SGAs. Similarly, the higher odds of having a major adverse outcome with SGAs are consistent with the higher rates of intubation and ventilation, since by definition the use of such interventions constitutes a major adverse outcome. While low-potency FGAs are also associated with CNS depression,[20] the low-potency FGAs in our sample, chlorpromazine, mesoridazine, and thioridazine, comprise slightly less than 50% of the overall FGA sample. Thus, the SGA sample still appears relatively weighted toward CNS-depressing agents compared to the FGAs.

Hypotension was a common side effect of both FGAs and SGAs, but the odds of hypotension being involved in a case were significantly higher for the SGAs. Antipsychotic-induced hypotension is usually associated with α_1 adrenergic blockade,[20] which among FGAs is more pronounced for the low-potency drugs. As noted above, these drugs made up about half of the FGA sample. Among the SGAs, quetiapine, olanzapine, and risperidone all have significant α_1 adrenergic blockade,[8] and all 3 drugs had hypotension as one of the most common symptoms reported. As these 3 drugs collectively make up 95% of our SGA sample, it is not surprising that the odds of hypotension were greater for the SGAs than for the FGAs. The increased odds of IV fluid use for SGA ingestions may reflect attempts to treat the observed hypotension, although there was no significant difference in vasopressor use between SGA and FGA cases.

The odds of dystonia and rigidity were both greater for FGAs than SGAs, likely a result of the FGAs' antagonism of postsynaptic dopamine receptors in the basal ganglia without the SGAs' mediating effect of serotonergic antagonism on the presynaptic dopaminergic cells.[6] The higher odds of possible or likely NMS cases observed

Table 4. Frequency of Adverse Outcomes, Symptoms, and Treatments by Specific Drug, N (%)[a]

Drug	No. of cases	Outcome: Minor Adverse Effect	Moderate Adverse Effect	Major Adverse Effect	Death	Respiratory Depression	Coma	Hypotension
Second-generation antipsychotic								
Aripiprazole	17	7 (41.2)	10 (58.8)					1 (5.9)
Clozapine	37	16 (43.2)	17 (46.0)	4 (10.8)		2 (5.4)	5 (13.5)	3 (8.1)
Olanzapine	333	151 (45.4)	155 (46.6)	27 (8.1)		12 (3.6)	34 (10.2)	21 (6.3)
Quetiapine	939	407 (43.3)	420 (44.7)	109 (11.6)	3 (0.3)	49 (5.2)	96 (10.2)	165 (17.6)
Risperidone	220	121 (55.0)	96 (43.6)	3 (1.4)			1 (0.5)	29 (13.2)
Ziprasidone	22	14 (63.6)	8 (36.4)					2 (9.1)
Total no. of second-generation antipsychotics	1568	716	706	143	3	63	136	221
First-generation antipsychotic								
Chlorpromazine	117	70 (59.8)	40 (34.2)	7 (6.0)		4 (3.4)	8 (6.8)	10 (8.6)
Fluphenazine	25	12 (48.0)	13 (52.0)					
Haloperidol	99	36 (36.4)	60 (60.6)	3 (3.0)		2 (2.0)	2 (2.0)	8 (8.1)
Molindone	4	1 (25.0)	3 (75.0)					1 (25.0)
Mesoridazine	3	2 (66.7)		1 (33.3)				
Perphenazine	33	13 (39.4)	20 (60.6)					2 (6.1)
Pimozide	1		1 (100)					1 (100)
Thioridazine	82	40 (48.8)	33 (40.2)	9 (11.0)		1 (1.2)	5 (6.1)	10 (12.2)
Thiothixene	26	15 (57.7)	9 (34.6)	2 (7.7)			1 (3.9)	2 (7.7)
Trifluoperazine	15	8 (53.3)	6 (40.0)	1 (6.7)			1 (6.7)	
Zuclopenthixol	2		2 (100)					
Total no. of first-generation antipsychotics	407	197	187	23	0	7	17	34

[a]Percentages of symptoms and treatments do not sum to 100% since a given case could involve multiple symptoms and treatments and not all possible symptoms and treatments coded by California Poison Control System are included in this table.
Abbreviation: NMS = neuroleptic malignant syndrome.

with the FGAs may also be accounted for by this same mechanism of D_2 receptor antagonism without serotonergic mediation, although the pathophysiology of NMS is incompletely understood.[21,22]

Although our study did not detect significant differences in QRS widening or QT prolongation between SGAs and FGAs, this finding must be tempered by the fact that, for the large majority of the cases, no QRS or QT information was available for analysis. A substantial proportion of the FGA major adverse effect cases were related to cardiac conduction abnormalities and usually involved thioridazine, a drug well known for its quinidine-like effects on cardiac conductance.[23] In contrast, data on potential cardiac conduction disturbances by SGAs were not as well established until recently.[24,25] Because QRS and QT information was not routinely collected by poison center specialists for the cases, the cardiac conduction results could be subject to reporting bias: clinicians contacting the CPCS and poison center specialists collecting information may have paid more attention to potential cardiac problems by the FGAs than the SGAs.

No cases of serotonin syndrome were detected in our study using Hunter Serotonin Toxicity Criteria; however, several factors mitigate this finding. The Hunter Serotonin Toxicity Criteria rely heavily on specific neurological findings (e.g., spontaneous, ocular, or inducible clonus; hyperreflexia) to make the diagnosis. Clinicians contacting the CPCS may not have performed these diagnostic maneuvers to assess for serotonin syndrome. Similarly, because information about clonus or hyperreflexia is not routinely collected by poison center specialists, cases in which a tremor was reported may in fact have involved clonus or hyperreflexia without specifically being recorded.

While 2 of the 3 deaths observed in our sample were attributed to quetiapine, deaths from overdose of risperidone,[26] olanzapine,[27] and clozapine[28] have all been reported, as well as a pediatric case involving ziprasidone.[29] Both quetiapine-related deaths in our study were associated with respiratory depression and were complicated by aspiration pneumonia. Other researchers have suggested this is the typical clinical course for fatal SGA overdoses.[8,30] Deaths from FGAs have been well documented[23,31,32]; however, none were observed in our study.

There are several limitations to this study. The number of cases in our study involving a particular drug is likely to be a function of its relative prevalence in the United States and not just its potential for toxicity. Furthermore, our study only included cases in which CPCS was contacted. An unknown number of other cases may have been managed without coming to the attention of CPCS, leaving the frequency and severity of cases in this retrospective study subject to reporting bias. For example, antipsychotic-induced dystonia is an easily treatable condition, but, subjectively, dystonia can be very distressing for the patient and the treating physician. This distress could lead to a variable threshold for contacting CPCS for assistance. In contrast, clinicians might feel relatively

Symptom								Treatment			
Long QT	Wide QRS	Dystonia	Rigidity	Rhabdomyolysis	Fever	Possible or Likely NMS	Seizure	Intubation	Ventilation	Intravenous Fluids	Vasopressors
3 (17.7)		6 (35.3)								3 (17.7)	
		2 (5.4)	1 (2.7)	1 (2.7)		1 (2.7)	3 (8.1)	8 (21.6)	8 (21.6)	12 (32.4)	
8 (2.4)	2 (0.6)	6 (1.8)	2 (0.6)	2 (0.6)	7 (2.1)	1 (0.3)	6 (1.8)	51 (15.3)	35 (10.5)	101 (30.3)	3 (0.9)
48 (5.1)	16 (1.7)	5 (0.5)		3 (0.3)	4 (0.4)		20 (2.1)	149 (15.9)	87 (9.3)	324 (34.5)	19 (2.0)
12 (5.5)	3 (1.4)	19 (8.6)	4 (1.8)	2 (0.9)	2 (0.9)	2 (0.9)	1 (0.5)	2 (0.9)	1 (0.5)	53 (24.1)	3 (1.4)
2 (9.1)		1 (4.6)						2 (9.1)	1 (4.6)	7 (31.8)	
73	21	39	7	8	13	4	30	212	132	500	25
6 (5.1)	1 (0.9)	4 (3.4)			1 (0.9)		1 (0.9)	11 (9.4)	7 (6.0)	27 (23.1)	1 (0.9)
1 (4.0)	1 (4.0)	7 (28.0)				1 (4.0)		1 (4.0)		3 (12.0)	
3 (3.0)		39 (39.4)	4 (4.0)	3 (3.0)	4 (4.0)	4 (4.0)	1 (1.0)	4 (4.0)	1 (1.0)	19 (19.2)	1 (1.0)
	1 (25.0)									3 (75.0)	
			1 (33.3)							1 (33.3)	
2 (6.1)		7 (21.2)	1 (3.0)				1 (3.0)			4 (12.1)	
1 (100)										1 (100)	
14 (17.1)	5 (6.1)	2 (2.4)			1 (1.2)		1 (1.2)	7 (8.5)	5 (6.1)	16 (19.5)	3 (3.7)
		4 (15.4)								5 (19.2)	
1 (6.7)		4 (26.7)						1 (6.7)		2 (13.3)	
		2 (100)									
28	8	69	6	3	6	5	4	24	13	81	5

more comfortable managing antipsychotic-induced sedation without assistance from CPCS and thus not seek additional support from CPCS unless the sedation was severe enough to cause respiratory compromise. The CPCS data also lack sufficient QRS or QT information to draw firm conclusions about cardiac conduction abnormalities for SGAs versus FGAs, as mentioned earlier.

Another limitation is that the CPCS data do not include measurements of the concentration of the drug involved in the ingestions. The total number of milligrams of a drug ingested is recorded in the CPCS database in a small minority of cases. Even in those cases, the ingested amount was usually based on the patient's self-report and not independently verified through witnessed ingestion or pill counts. Time of arrival to health care facilities and decontamination procedures after arrival varied among cases as well; thus, initially equivalent ingestions could still result in different final levels of absorption. None of the cases had a serum concentration of an FGA or SGA recorded. For these reasons, it is possible that the average doses involved in the cases are not equivalent between the SGAs and FGAs.

A final limitation is that there are substantial differences in receptor affinity and side effect profiles among the individual SGAs and FGAs. With such variability among drugs, it may seem inappropriate to compare an entire class of diverse agents against another class of diverse agents. Despite this diversity of individual drugs, however, the overwhelming majority of antipsychotic drugs prescribed in the United States are SGAs,[1] and the goal of this study was to determine, from a safety standpoint, whether that preference for this class of drugs is warranted.

In the treatment of depression, the newer generation of antidepressants, the selective serotonin reuptake inhibitors (SSRIs), have been favored over the older tricyclic antidepressants (TCAs).[33] This preference is not due to superior efficacy for SSRIs over TCAs,[33,34] but rather due to other factors: a more benign side effect profile for SSRIs compared to TCAs[33,34] and markedly improved safety of SSRIs in acute overdose compared to TCAs.[35,36] As the risk for suicide among schizophrenic patients is also high, safety in acute overdose appears to be a reasonable factor to consider when selecting an antipsychotic medication. Unlike the SSRIs versus the TCAs, however, we do not find a clear safety advantage for SGAs over FGAs following acute ingestion of a toxic dose.

In conclusion, our review of 1975 cases of acute SGA or FGA toxic ingestion revealed that the odds of a major adverse outcome or death were significantly higher with SGAs than with FGAs, suggesting that the SGAs are not safer in acute overdose. The odds of respiratory depression, coma, and hypotension were higher with the SGAs, whereas the odds of dystonia and rigidity were higher with the FGAs. Adverse reactions produced by SGAs, such as CNS depression, may seem more mundane than the dystonia or rigidity that FGAs can produce. However, respiratory depression and coma can be life threatening,

and the drugs that cause them should be prescribed with caution.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), molindone (Moban), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal and others), thiothixene (Navane and others), ziprasidone (Geodon).

REFERENCES

1. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005 Sep;353(12):1209–1223
2. Weiden P, Aquila R, Standard J. Atypical antipsychotic drugs and long-term outcome in schizophrenia. J Clin Psychiatry 1996; 57(suppl 11):53–60
3. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2000;60:553–564
4. Brown CS, Markowitz JS, Moore TR, et al. Atypical antipsychotics, pt 2: adverse effects, drug interactions, and cost. Ann Pharmacother 1999;33: 210–217
5. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. J Clin Psychiatry 1999;60(suppl 10):5–14
6. Kinon BJ, Lieberman JA. Mechanisms of action of atypical antipsychotic drugs: a critical analysis. Psychopharmacology (Berl) 1996;124(1–2): 2–34
7. Jones PB, Barnes TRE, Davies L, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry 2006; 63(10):1079–1087
8. Burns MJ. The pharmacology and toxicology of atypical antipsychotic agents. J Toxicol Clin Toxicol 2001;39(1):1–14
9. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156: 1686–1696
10. Henderson DC, Cagliero E, Copeland PM, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotics: a frequently sampled intravenous glucose tolerance test and minimal model analysis. Arch Gen Psychiatry 2005;62:19–28
11. Koro CE, Fedder DO, L'Italien GJ, et al. An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. Arch Gen Psychiatry 2002; 59(11):1021–1026
12. Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: international suicide prevention trial. Arch Gen Psychiatry 2003;60:82–91
13. Lai MW, Klein-Schwartz W, Rodgers GC, et al. 2005 Annual Report of the American Association of Poison Control Centers' national poisoning and exposure database. Clin Toxicol (Phila) 2006;44:803–932
14. Watson WA, Litovitz TL, Belson MG, et al. The Toxic Exposure Surveillance System (TESS): risk assessment and real-time toxicovigilance across United States poison centers. Toxicol Appl Pharmacol 2005; 207(2):604–610
15. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal." J Cardiovasc Electrophysiol 2006;17:333–336
16. Bazett HC. An analysis of time relations of electrocardiograms. Heart 1920;7:353–367
17. Josephson ME. Clinical Cardiac Electrophysiology: Techniques and Interpretations. 3rd ed. Philadelphia, Pa: Lippincott and Wilkins; 2002
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
19. Dunkley EJC, Isbister GK, Sibbritt D, et al. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. Q J Med 2003;96:635–642
20. Owens DG. Adverse effects of antipsychotic agents: do newer agents offer advantages? Drugs 1996;51(6):895–930
21. Levinson JL. Neuroleptic malignant syndrome. Am J Psychiatry 1985; 142(10):1137–1145
22. Hasan S, Buckley P. Novel antipsychotics and the neuroleptics malignant syndrome: a review and critique. Am J Psychiatry 1998;155:1113–1116
23. Reilly JG, Ayis SA, Ferrier IN, et al. Thioridazine and sudden unexplained death in psychiatric inpatients. Br J Psychiatry 2002;180: 1515–1522
24. Stollberger C, Huber JO, Finsterer J. Antipsychotic drugs and QT prolongation. Int Clin Psychopharmacol 2005;20(5):243–251
25. Harrigan EP, Miceli JJ, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. J Clin Psychopharmacol 2004;24(1):62–69
26. Brown K, Levy H, Brenner C, et al. Overdose of Risperidone. Ann Emerg Med 1993;22:1908–1910
27. Elian AA. Fatal overdose of olanzapine. Forensic Sci Int 1998;91: 231–235
28. Reith D, Monteleone PR, Whyte IM, et al. Features and toxicokinetics of clozapine in overdose. Ther Drug Monit 1998;20:92–97
29. Scahill L, Blair J, Leckman JF, et al. Sudden death in a patient with Tourette syndrome during a clinical trial of ziprasidone. J Psychopharmacol 2005;19(2):205–206
30. LeBlaye I, Donatini B, Hall M, et al. Acute overdosage with clozapine: a review of the available clinical experience. Pharmaceutical Med 1992; 6:169–178
31. Hollister LE, Kosek JC. Sudden death during treatment with phenothiazine derivatives. JAMA 1965;192:1035–1038
32. Ray WA, Meredeith S, Thapa PB, et al. Antipsychotics and the risk of sudden cardiac death. Arch Gen Psychiatry 2001;58:1161–1167
33. Steffens DC, Krishnan KRR, Helms IM. Are SSRIs better than TCAs? comparison of SSRIs and TCAs: a meta-analysis. Depress Anxiety 1998;6(1):10–18
34. Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. Depress Anxiety 1998;7(suppl 1):11–17
35. Barbey JT, Roose SP. SSRI safety in overdose. J Clin Psychiatry 1998; 59(suppl 15):42–48
36. Stoner SC, Marken PA, Watson WA, et al. Antidepressant overdoses and resultant emergency department services: the impact of SSRIs. Psychopharmacol Bull 1997;33:667–670

Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Marlene Freeman, M.D., at mfreeman@psychiatrist.com.

July 23, 2012 **Paul S. Appelbaum, MD**

Expert Testimony by Deposition or Courtroom Testimony Over the Last 5 Years

Fleming v. MUSC, Civil Action #06-CP-10-2971, Court of Common Pleas, Ninth Judicial Circuit, County of Charleston, SC, May 16, 2008 (deposition—retained by plaintiff).

Caulfield v. Imagine Advisors, Inc. No. 07 Civ 1257 (DC), U.S. District Court, Southern District of NY, September 2 and 3, 2008 (deposition—retained by plaintiff).

Pringle v. SC Dept. of Corrections, Court of Common Pleas, Civil Action #07-CP-03-360, County of Allendale, SC, December 17, 2009 (deposition—retained by plaintiff).

Mulligan v. Rosedale, Jefferson County (KY) Circuit Court, No. 09-CI-03494, March 1, 2011 (deposition—retained by defendant).

Mulligan v. Rosedale, Jefferson County (KY) Circuit Court, No. 09-CI-03494, March 1, 2012 (trial testimony—retained by defendant).

July 24, 2012 **Paul S. Appelbaum, MD**

My fees to date, previous bills have totaled $6750; together with the latest bill of $2375, the total to date comes to $10,125.

My hourly rate is $500.00.